IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Confirmation No. 7978
Serial No. 10/559,835	Group Art Unit: 1633
Takehisa Matsuda	Examiner:LEAVITT,MARIA GOMEZ

Filed: December 6, 2005

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patents and Trademarks

Sir,

I, Keigo Hanada declare that:

I was born in Kagoshima Prefecture, Japan, in 1959;

I am a citizen of Japan and a resident of Kusatsu-shi, Shiga, Japan;

I received the license of Doctor of Veterinary Medicine in 1984.

I received my doctor degree on the study of "Immune responses in newly developed short-lived SAM mice. III. Genetic controls of the defective helper T cell activity in vitro primary antibody response." at Kyoto University, Kyoto, Japan, in 1990,

I was appointed as Assistant Professor of Department of Microbiology and Immunology at Shimane Medical Collage, Shimane Japan, in 1989,

I have worked as Senior Scientist and Manager of Central Research Laboratory of Research and Development Division at

Kaken Pharmaceutical Co. Ltd. in Japan from 1990 till 2003;

I was appointed as Senior Scientist of Discovery & Pharmacology Research Laboratory of Research and Development Division at Tanabe Seiyaku Co. Ltd. Japan, in 2003;

I was appointed as Principal Scientist and Section Manager of Pharmacology Research Laboratory of Research and Development Division at Tanabe Seiyaku Co. Ltd. Japan, in 2005;

I was appointed as Director of Research and Development Division at Kringle Pharma, Inc. Japan in 2006;

I was a visiting Scientist of Department of Biology of Case Western Reserve University, U.S.A., from 1995 till 1997;

I was a part-time Assistant Professor of Dept. of Ultrastructural Research of Institute for Frontier Medical Science at Kyoto University, Kyoto Japan from 1998 till 2002;

I was an Associate Professor of Center for Advanced Science and Innovation of Osaka University, Osaka Japan from 2007 till 2008;

I reported the following papers:

1. Yonezu T., Tsunasawa S., Higuchi K., Kogishi K., Naiki H., Hanada K., Sakiyama F., and Takeda T.:
   A molecular-pathologic approach to murine senile amyloidosis; Serum precursor-Apolipoprotein A-II variant ($Pro^5 \rightarrow Gln$) presents only in the senile amyloidosis-prone SAM-P/1 and SAM-P/2 mice. ***Laboratory Investigation***, 57: 65-70, 1987.

2. Hosokawa T., Hosono M., Hanada K., Aoike A., Kawai K., and

Takeda T.:
Immune responses in newly developed short-lived SAM mice. II. Selectively impaired T-helper cell activity in in vitro antibody response. ***Immunology***, 62: 425-429, 1987.

3. Mitsuoka A., Hanada K.:
In vivo immune reactivities in Senescence Accelerated Mouse (SAM)
In: *Proceedings of the First SAM Kyoto Symposium.* Takeda T. (ed.), p11-20, Fuji Printing Business Company, Kyoto, 1988.

4. Hosono M., .Hosokawa T., and Hanada K.:
In vitro immune activities of short-lived SAM mice: Early loss of helper T cell function in primary antibody responses
In: *Proceedings of the First SAM Kyoto Symposium.* Takeda T. (ed.), p21-30, Fuji Printing Business Company, Kyoto, 1988.

5. Hanada K., Hosono M., Hosokawa T., Chen W.H., Tsuboyama T., and Takeda T.:
Immune responses in newly developed short-lived SAM mice. III. Genetic controls of the defective helper T cell activity in in vitro primary antibody response. ***Immunology***, 68: 540-548, 1989.

6. Tusboyama T., Matsushita M., Okumura H., Yamamuro T., Hanada K., and Takeda T.:
Modification of strain-specific femoral bone density of bone marrow chimerism in mice; A study on spontaneously

osteoporotic mouse (SAM-P/6). ***Bone***, 10: 269-277, 1989.

7. Umezawa M., Hanada K., Hosono M., Hosokawa T., Chen W.H., Hosokawa M., and Takeda T.:
Effect of dietary restriction on age related immune dysfunction in the Senescence Accelerated Mouse (SAM). ***J. Nutri.***, 120: 1393-1400, 1990.

8. Hanada K., Katoh H., Hosokawa T., Hosono M., and Takeda T.:
Immune responses in newly developed short-lived SAM mice IV. Chromosomal location of a gene controlling defective helper T cell activity. ***Immunology***, 74: 160-164, 1991.

9. Kawaguchi K., Kurokawa T., Ogata E., Matumoto T., Hanada K., Hiyama Y., and Tamura M.:
Stimulation of fracture repair by recombinant human basic fibroblast growth factor in normal and streptozotocin-diabetic rats. ***Endocrinology***, 135: 774-781, 1994.

10. Toichi E., Hanada K., Katoh H., Hosokawa T., and Hosono M.:
Immune activities in SAM mice.
In: *The SAM model of Senescence*, Takeda T. (ed.), p41-46. Excerpta Media, Elsevier Science B.V., Amsterdam, 1994.

11. Hosokawa T., Hosono M., Hanada K., Toichi E., and Takeda T.:
Age-associated early decline in immune activities in the senescence accelerated mouse (SAM): Impaired T-helper cell

activity in in vitro primary and secondary antibody response.
In: *The SAM model of Senescence*, Takeda T. (ed.), p163-166. Excerpta Media, Elsevier Science B.V., Amsterdam, 1994.

12. Hanada K., Katoh H., Toichi E., Hosokawa T., Takeda T., and Hosono M.:
Genetic control of defective helper T cell activity in in vitro antibody response in short-lived SAM mice.
In: *The SAM model of Senescence*, Takeda T. (ed.), p171-174. Excerpta Media, Elsevier Science B.V., Amsterdam, 1994.

13. Toichi E., Hanada K., Hosono M., Hosokawa T., Hosokawa M., Baba M., and Takeda T.:
Early decline of T cell function in humoral immunity and long-lasting inflammatory T cell activity in aging SAM mice.
In: *The SAM model of Senescence*, Takeda T. (ed.), p175-178. Excerpta Media, Elsevier Science B.V., Amsterdam, 1994.

14. Nakamura T., Hanada K., Tamura M., Shibanushi T., Nigi. H., Tagawa M., Fukumoto S., and Matsumoto T.:
Stimulation of endosteal bone formation by systemic injections of basic fibroblast growth factor in normal rats.
Endocrinology, 136: 1276-1284, 1995.

15. Nakamura K., Kurokawa T., Kato T., Okazaki H., Mamada K., Hanada K., Hiyama Y., Aoyama I., Nakamura T., and Tamura M.:

Local application of basic fibroblast growth factor into the bone increases bone mass at the applied site in rabbits. ***Arch. Orthop. Trauma. Surg.***, 115: 344-346, 1996.

16. Hosono M., Hanada K., Toichi E., Naiki H., and Hosokawa M.:
Immune abnormality in relation to nonimmune disease in SAM mice. ***Experimental Gerontology***, 32: 181-195, 1997.

17. Toichi E., Hanada K., Hosono M., Hosokawa T., Hosokawa M., Baba M., Imamura S., and Takeda T.:
Age-related decline in humoral immunity caused by the selective loss of T_H cells and decline in cellular immunity caused by the impaired migration of inflammatory cells without a loss of T_{DTH} cells in SAMP1 mice. ***Mech. Ageing Dev.***, 99: 199-217, 1997.

18. Hanada K., Dennis J.E., and Caplan A.I.:
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19. Nakamura K., KurokawaT., Kawaguchi H., Kato T., Hanada K., Hiyama Y., Aoyama I., Nakamura T., Tamura M., and Matsumoto T.:
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in rats. ***Rev. Rhum.***, (English ed.) 64: 101-105, 1997.

20. Nakamura K., Kawaguchi H., Aoyama I., Hanada K., Hiyama Y., Awa T., Tamura M., and Kurokawa T.:
Stimulation of bone formation by intraosseous application of recombinant basic fibroblast growth factor in normal and ovariectomized rabbits. ***J. Orthop. Res.***, 15: 307-313, 1997.

21. Fujimoto E., Mizoguchi A., Hanada K., Yajima M., and Ide C.:
Basic fibroblast growth factor promotes extension of regenerating axons of peripheral nerve. In vivo experiments using a Schwann cell basal lamina tube model. ***J. Neurocytol.***, 26: 511-528, 1997.

22. Kato T., Kawaguchi H., Hanada K., Aoyama I., Hiyama Y., Nakamura T., Kuzutani K., Tamura M., Kurokawa T., and Nakamura K.:
Single local injection of recombinant basic fibroblast growth factor stimulates healing of segmental bone defects in rabbits. ***J. Orthop. Res.***, 16: 654-659, 1998.

23. Nakamura K., Kurokawa T., Aoyama I., Hanada K., Tamura M., and Kawaguchi K.:
Stimulation of bone formation by intraosseous injection of basic fibroblast growth factor in ovariectomized rats. ***Int. Orthop.***, 22: 49-54, 1998.

24. Hanada K., Solchaga L.A., Caplan A.I., Hering T.M., Goldberg V.M., Yoo J.U., and Johnstone B.:
BMP-2 induction and TGF-β1 modulation of rat periosteal cell chondrogenesis. ***J. Cell. Biochem.***, 81: 284-294, 2001.

25. Furuya K., Yamamoto N., Nejishima H., Ichikawa K., Amano S., Tsunashima M., Sumita Y., Inoguchi K., Miyakawa M., Nakamura T., and Hanada K.:
Novel, non-steroidal selective androgen receptor modulators (SARMs) increase bone mass and reduce androgenic virilizing effects in adult osteoporotic rats. ***J. Bone Miner. Res.***, 16:S148, 2001.

26. Yamamoto N., Furuya K., and Hanada K.:
Progressive development of the osteoblast phenotype during differentiation of osteoprogenitor cells derived from fetal rat calvaria : Model for *in vitro* bone formation. ***Biol. Pharm. Bull.*** 25(4): 509-515, 2002.

27. Hanada K, Furuya K., Yamamoto N., Nejishima H., Ichikawa K., Amano S., Sumita Y., Oguro N., Miyakawa M., and Nakamura T.,:
Novel, non-steroidal selective androgen receptor modulators (SARMs) have bone anabolic activity in adult osteoporotic rats. ***J. Bone Miner. Res.***, 17: S483, 2002.

28. Hanada K., Furuya F., Yamamoto N., Nejishima H., Ichikawa K., Nakamura T., Miyakawa M., Amano S., Sumita Y., and

Oguro N.:
Bone anabolic effects of S-40503, a novel nonsteroidal selective androgen receptor modulator (SARM), in rat models of osteoporosis ***Biol. Pharm. Bull.***, 26(11):1563-1569, 2003.

29. Hayata D., Fukuta K., Matsumoto K., Adachi E., Hanada K., Adachi K., and Nakamura T.:
Generation of engineered recombinant hepatocyte growth factor cleaved and activated by Genenase I. ***J. Biotechnol.***, in press.

I received the following awards:

1. SIROT Award for "Bone formation by Intraosseous Application of Basic Fibroblast Growth Factor in Ovariectomized Rats", The 7th World Congress, Amsterdam, The Netherlands, August 19, 1996.

2. Young Investigator Award for "Novel, Non-steroidal Selective Androgen Receptor Modulators (SARMs) Increase Bone Mass and Reduce Androgenic Virilizing Effects in Adult Osteoporotic Rats", 23rd Annual Meeting of The American Society for Bone and Mineral Research (ASBMR), Phoenix, Arizona, USA, October 12-16, 2001.

I declare the followings:

1. As shown in lines 15-20 on page 21 of the specification,

the fibrous protein of the present invention serves as a carrier of the cells. Containing the fibrous protein permits the cell-containing preparation to be formed into various shapes such as a sheet, sphere and tube, and the preparation can be administered to all sites in the body.

2. The mesh sheet of the present invention maintains strength of the cell-containing preparation, although the fibrous protein comprises a culture medium suitable for culturing the cells. By including a culture medium in the fibrous protein, nutrients can be supplied to the cells in the cell-containing preparation, leading to stable and longer survival of the cells when the cell-preparation is administered to the living body (See lines 7-19 on page 22 of the specification). In addition, the mesh sheet allows cells to release in the opposite direction of the sheet, and cells can be efficiently arrived at the desired site of the living body (See figure 1 of the present application).

3. Using epithelial cells of the oral mucosa in the cell-containing preparation of the present invention achieves the following advantages.

(i) Epithelial cells of the oral mucosa can be easily harvested without invasion to a patient such as abdominal operation.

(ii) Since epithelial cells of the oral mucosa proliferate fast, healing of the site of the oral cavity wherein epithelial cells are removed is fast.

(iii) Since epithelial cells of the oral mucosa proliferate

fast, harvest of a small amount of cells is sufficient for preparing cell-containing preparation.

(iv) Epithelial cells of the oral mucosa proliferate to form multilayered cells. Multilayered cells are unlikely to become extinct, thereby multilayered cells in the cell-containing preparation can release NK4 over a long period of time.

4. Fibroblasts form multilayered cells.

It is declared by the undersigned that all statements made herein of undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Date: September 8, 2008 Keigo Hanada

Keigo Hanada,